

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Udo Baron, Manfred Gossen
and Hermann Bujard

Serial No.: (Divisional of Serial No. 09/557,027)

Filed: August 3, 2001 (herewith)

For: *Transgenic Organisms Having Transcriptional
Activators with Graded Ttransactivation Potential (as
amended)*

Attorney Docket No. BBI-088CPADV2

Group Art Unit: Not Yet Assigned

Examiner: Not Yet Assigned

**Commissioner for Patents
BOX PATENT APPLICATION
Washington, D.C. 20231**

CERTIFICATION UNDER 37 CFR 1.10

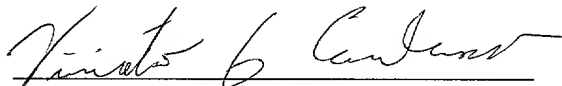
Date of Deposit: August 3, 2001

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I hereby certify that this 37 CFR 1.53(b) request and the documents referred to as attached therein are being deposited with the United States Postal Service on the date indicated above in an envelope as "Express Mail Post Office to Addressee" service under 37 CFR 1.10 and addressed to the Commissioner for Patents, Box Patent Application, Washington, D.C. 20231.

Viriato G. Cardoso

Name of Person Mailing Paper


Signature of Person Mailing Paper

PRELIMINARY AMENDMENT

Dear Sir:

Prior to examination of the above-identified application, please amend the application as follows:

In the Specification

The title has been amended as follows:

**--Transgenic Organisms Having Transcriptional Activators With
Graded Transactivation Potential--**

Please insert into the instant specification substitute pages 38-43 filed herewith, setting forth a revised Sequence Listing, and renumber the pages of the Specification as necessary.

In the Figures

Please replace Figure 1 with the revised Figure 1 enclosed herewith.

In the Claims

Please cancel claim 1 without prejudice.

Please add new claims 32-50, as follows:

--32. A non-human transgenic organism comprising a transgene comprising a nucleic acid molecule encoding a fusion protein which activates transcription, the fusion protein comprising a first polypeptide comprising a DNA binding domain operatively linked to a second polypeptide comprising a transcriptional activation domain, wherein the transcriptional activation domain comprises at least one copy of a mutated acidic region of herpes simplex virus virion protein 16 (HSV VP16), the mutated acidic region consisting of amino acid positions 436 to 447 of HSV VP16 (SEQ ID NO: 1) and having an amino acid substitution at position 442 as compared to wild type HSV VP16, the transgene being in a form suitable for expression of the fusion protein in cells of the non-human transgenic organism.

33. The transgenic organism of claim 32, wherein the mutated acidic region of HSV VP16 has the amino acid sequence of SEQ ID NO: 2.

34. The transgenic organism of claim 32, wherein the mutated acidic region of HSV VP16 has the amino acid sequence of SEQ ID NO: 3.
35. The transgenic organism of claim 32, wherein the transcriptional activation domain comprises the amino acid sequence of SEQ ID NO: 4.
36. The transgenic organism of claim 32, wherein the transcriptional activation domain comprises the amino acid sequence of SEQ ID NO: 5.
37. The transgenic organism of claim 32, wherein the transcriptional activation domain comprises the amino acid sequence of SEQ ID NO: 6.
38. The transgenic organism of claim 32, wherein the transcriptional activation domain comprises the amino acid sequence of SEQ ID NO: 7.
39. The transgenic organism of claim 32, wherein the transcriptional activation domain comprises the amino acid sequence of SEQ ID NO: 8.
40. The transgenic organism of claim 32, wherein the first polypeptide is a Tet repressor.
41. The transgenic organism of claim 32, wherein the first polypeptide is a mutated Tet repressor that binds to *tetO* sequences in the presence, but not in the absence, of tetracycline or a tetracycline analogue.
42. The transgenic organism of claim 32, wherein first polypeptide is selected from the group consisting of GAL4, LexA, LacR and steroid hormone receptors.
43. A non-human transgenic organism comprising a transgene comprising a nucleic acid molecule encoding a fusion protein which activates transcription, the fusion protein comprising a first polypeptide comprising a DNA binding domain operatively linked to a second polypeptide comprising a transcriptional activation domain, wherein the transcriptional activation domain consists of three copies of an acidic region of herpes simplex virus virion protein 16 (HSV VP16), the acidic region consisting of amino acid

positions 436 to 447 of HSV VP16 (SEQ ID NO:1), the transgene being in a form suitable for expression of the fusion protein in cells of the non-human transgenic organism.

44. The transgenic organism of claim 43, wherein the first polypeptide is a Tet repressor.
45. The transgenic organism of claim 43, wherein the first polypeptide is a mutated Tet repressor that binds to *tetO* sequences in the presence, but not in the absence, of tetracycline or a tetracycline analogue.
46. The transgenic organism of claim 43, wherein first polypeptide is selected from the group consisting of GAL4, LexA, LacR and steroid hormone receptors.
47. A non-human transgenic organism comprising a transgene comprising a nucleic acid molecule encoding a fusion protein which activates transcription, the fusion protein comprising a first polypeptide comprising a DNA binding domain operatively linked to a second polypeptide comprising a transcriptional activation domain, wherein the transcriptional activation domain consists of four copies of an acidic region of herpes simplex virus virion protein 16 (HSV VP16), the acidic region consisting of amino acid positions 436 to 447 of HSV VP16 (SEQ ID NO:1), the transgene being in a form suitable for expression of the fusion protein in cells of the non-human transgenic organism.
48. The transgenic organism of claim 47, wherein the first polypeptide is a Tet repressor.
49. The transgenic organism of claim 47, wherein the first polypeptide is a mutated Tet repressor that binds to *tetO* sequences in the presence, but not in the absence, of tetracycline or a tetracycline analogue.
50. The transgenic organism of claim 47, wherein first polypeptide is selected from the group consisting of GAL4, LexA, LacR and steroid hormone receptors.--

REMARKS

Claim 1 was pending in the instant application and has now been cancelled without prejudice. New claims 32-50 have been added and thus are pending. Support for the new claims can be found in the specification and in the claims of the parent applications as originally filed.

The title has been amended to more clearly reflect the subject matter being claimed. Applicants submit herewith a "VERSION WITH MARKINGS TO SHOW CHANGES MADE", set forth as Appendix A, indicating the specific amendments made to the title.

Figure 1 and the Sequence Listing have been amended to delete the initial proline residue from the minimal VP16 domain shown in Figure 1 and the Sequence Listing, as this initial proline residue is not derived from the VP16 sequence. Support for this amendment may be found, for example, at page 29, lines 18-20, which states that the minimal activation domains of the invention were derived from VP16 and comprise positions 436 to 477 according to Seipel et al. Seipel et. al. is incorporated into the specification in its entirety at page 28, lines 30-32. This reference teaches the amino acid sequence of the entire VP16 molecule and utilizes the same numbering system for the amino acid residues as is used in the instant specification. One of ordinary skill in the art would be able to determine from Seipel et al. that the initial proline shown in Figure 1 as originally filed and in the Sequence listing prior to amendment is not derived from VP16; residue 435 of VP16 is a histidine. The proline residue was generated when constructing the vector surrounding the VP16 minimal domain; one skilled in the art would be cognizant of the fact that this initial proline derived from the cloning method used and that other amino acids could alternatively be positioned upstream of the alanine according to the desired restriction site or linker region in the surrounding vector. For example, the specification at page 30, lines 4-5, states that "[t]he protruding 5' ends of the double stranded oligonucleotides are compatible with the cleavage site of restriction endonuclease XmaI." It would be readily apparent to the ordinary skilled artisan that other restriction sites could be used for cloning depending on the vector chosen, in which case the 5' ends of the oligonucleotides would differ, leading potentially to a different amino acid residue from proline upstream of Ala-436 of VP16. The correct

sequence for VP16 positions 436 to 447 begins at the alanine residue shown in amended Figure 1 and in the amended sequence listing.

In accordance with 37 C.F.R. §1.82, Applicants submit herewith substitute pages 38-43 which contain a revised Sequence Listing for the parent application that complies with the sequence listing rules and that recites the correct amino acid sequence for VP16 positions 436-477. Applicants have also amended the specification to include substitute pages 38-43 and have requested renumbering of the pages accordingly.

No new matter has been added to the claims or specification.

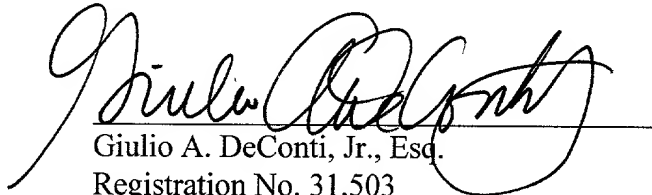
CONCLUSION

All pending claims are believed to be in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call Applicants' Attorney at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP

Date: August 3, 2001


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APPENDIX A

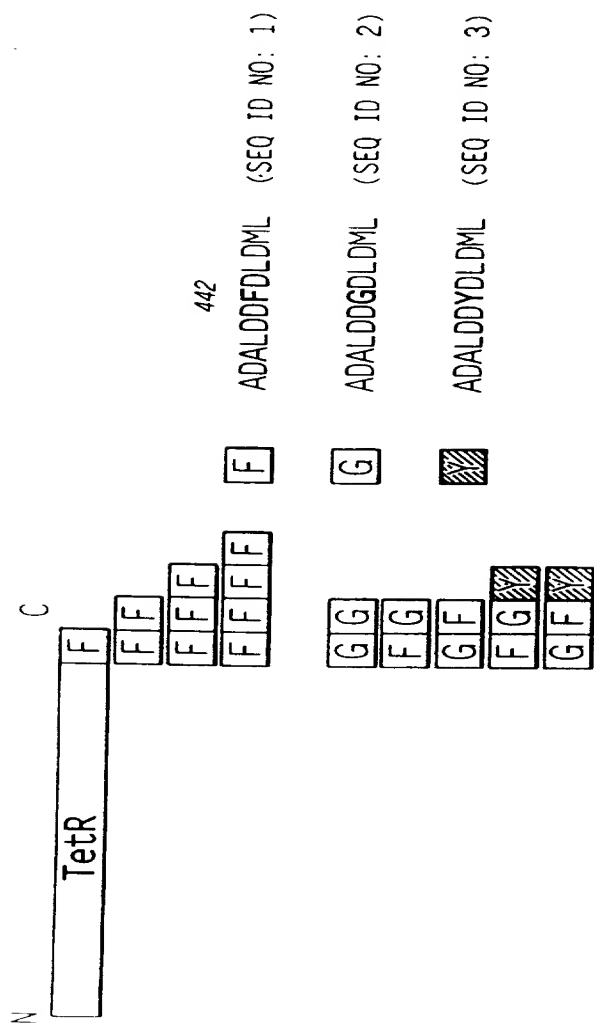
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RECEIVED



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